Progress (interim) Report

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Title of Project:
Channelling into mechanisms of neurological disease: An in-depth study of abnormal nerve excitability in neurological disorders (epilepsy and chronic neuropathic pain).

Summary:

Nerve cell membranes are electrically active. Ion channels are membrane-bound proteins which allow the passage of charged particles (ions) across the membrane of nerve cells. Dysfunction of ion channels (genetic or acquired) can result in abnormal nerve excitability. The symptoms of ion channel dysfunction in the nervous system are widely varied and depend upon the site of the specific channel affected, and the role of that channel in the membrane. Neurological features caused by ion channel dysfunction include seizures, ataxia, migraine, pain, epilepsy and stroke-like symptoms. Furthermore, several medications used to treat neurological disease (e.g. anticonvulsants, medications for neuropathic pain) exert their action via ion channel modulation. Hence, an understanding of ion channel function and disorders is relevant to every neurological subspecialty.

This **BRAIN FOUNDATION** grant focuses on ion channel dysfunction in conditions encountered commonly in neurological practise: epilepsy and neuropathic pain. The conditions share common physiologic features - that abnormal neuronal excitability plays a role in manifestation of the disease.

This project has 2 arms (i.e .pain and epilepsy); each arm with 2 research questions. The study is designed to advance understanding of the pathophysiology of both pain and epilepsy, while at the same time developing a tool with potential use in clinical practice to aid diagnosis, monitor treatment and serve as a biomarker of disease activity.

With regards to neuropathic pain:
1. Can peripheral nerve excitability studies detect altered Ih in patients with central neuropathic pain?
2. Can peripheral nerve excitability studies detect altered Ih in patients with peripheral neuropathic pain?

With regards to epilepsy:

3. Can nerve excitability studies predict seizure recurrence in patients with a first seizure?
4. Is there detectable peripheral nerve alteration in Ih in epilepsy patients carrying the HCN2 triple proline deletion?

Hypothesis vs Findings

This **BRAIN FOUNDATION** research gift complements the NHMRC Early Career Fellowship (completion due Dec 2017) and longitudinal recruitment is underway. Interim analysis is to be performed in December, 2016. Since commencing this project, we have been able to solidify and expand the scope of our project and collaborations, both locally and internationally. The **BRAIN FOUNDATION** research gift has also enabled us to develop infrastructure at the University of Sydney, attracting a research assistant (Chris Rofe, BSc), now trained in excitability studies and facilitating recruitment of patients to both arms and expanding our database of control subjects.

Increasingly, the importance of understanding the measurable impact of neuromodulatory agents (such as those used to treat neuropathic pain and epilepsy) on excitability studies is paramount to our interpretation of the results in this present study and related studies. This project has enabled us to establish a unique database of patients with idiopathic epilepsy on anticonvulsant monotherapy. Provisional analysis indicates that there is no statistically significant change in excitability studies in patients using monotherapy compared to controls. This is an important finding because currently published data outline that there are changes in excitability in patients treated with ion channel blockers in vivo (in particular, lignocaine and high dose, single bolus carbamazepine). Hence, one potential confounder for any study performed on a patient with epilepsy or pain taking neuromodulatory agents at the time of study is that the results may reflect the drug effect rather than the disease effect. However, unlike our present study, the published data are not representative of clinical practice or actual patient management and cannot really be extrapolated to our study cohort. With the emerging database created with the aid of this **BRAIN FOUNDATION** research gift, we are able to define that in vivo drug effect for oral agents is minimal, and not statistically significant. Hence, the results of the excitability studies in our group (and others) can be determined due to the disease effect. Expanding on this concept, this study will follow patients before commencement of neuromodulatory agents, during treatment and potentially, after treatment (off therapy where clinically indicated) in order to serve as their own ‘internal control’.

What these research outcomes mean

It is anticipated that the results of this project will define the role of HCN channel function in patients with epilepsy and chronic pain; disorders in which abnormal nerve excitability results in the condition. These findings will have implications for use of excitability studies in clinical practice and have a future role in the diagnosis, assessment and monitoring of these common neurological disorders.

With regards to the relevance of studies in neuropathic pain, I was invited to speak at the World Congress of Neurology in Chile to present the current clinical and research aspects of physiologic evaluation of painful neuropathies (Tomlinson SE. Loss and

gain of function mutations affecting nociception and paroxysmal pain disorders. Channelopathy symposium; World Congress of Neurology, Santiago, Chile, 2015).

As defined in the research proposal, we continue to develop the research collaboration with Professors Berkovic and Scheffer (University of Melbourne) evaluating excitability studies in patients with genetic epilepsy. With the aid of the **BRAIN FOUNDATION** research gift, we have been able to expand the scope of our initial proposed research into genetic epilepsy. We are now including longitudinal data in studies across different age groups to determine disease effect in the context of maturation effect. This is a particularly exciting aspect of the study, and the collaboration has been advantageously expanded to include paediatric arm (with Dr Michelle Farrar FRACP and Dr Cindy Lin PhD at University of NSW). I would hope the studies could define excitability in changes in children and adults with Dravets and GEFS+ and establish separation between phenotype at a young age, potentially with greater divergence as in older age groups in keeping with phenotype. It is hard to predict the results of course, but with modelling we may be able to establish physiologic basis for different phenotypes in same mutation (?compensation vs developmental variability?), potentially to explain variability in *in vitro* expression data. The aim would be to contribute to the understanding of the physiologic basis of the phenotype; which is much more meaningful than seeking a 'biomarker of disease'. Again, the database of patients on antiepileptic monotherapy will prove invaluable in analysing the results. We have a further research visit to study patients with monogenic epilepsy in October, 2016 and then likely to study the triple proline repeat cohort in November, 2016.

In a broader research setting, as a result of the profile of our current project funded by the **BRAIN FOUDNATION** in these common neurological conditions, I was invited to be a co-organiser, demonstrator and lecturer by Professor Hugh Bostock, FRS at the 8th International Nerve Excitability Workshop May 4-6 2016, United Kingdom. The remit for my involvement was to provide insight into translational research projects using basic science techniques in the clinical settings and provisional data for this project was discussed.